DOCTOR OF PHILOSOPHY

Cardiovascular events and mortality in systemic sclerosis: A study of the effect of Iloprost on these and on disease progression
The SSTEP Study (Systemic Sclerosis Trial of Events and Progression)

McSwiggan, Stephen John

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Stephen John McSwiggan

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University of Dundee

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Stephen John McSwiggan

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ABBREVIATIONS

ABI	Ankle brachial index
ACR	American College of Rheumatology
ACEi	Angiotensin-converting-enzyme inhibitor
ACA	Anti-centromere antibody
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
AR	Adverse reaction
ARA	American Rheumatology Association
AST	Aspartate transaminase
ATS	American Thoracic Society
AZO	Azathioprine
BMI	Body mass index
BP	Blood pressure
BSE	British Society of Echocardiography
cAMP	Cyclic adenosine monophosphate
CABG	Coronary artery bypasses graft
CAD	Coronary artery disease
CCB	Calcium channel blocker
CEC	Clinical Endpoints Committee
CHD	Coronary heart disease
CI	Confidence interval
CMV	Cytomegalovirus
CrCl	Creatinine clearance

CRF	Case report form
CO	Carbon monoxide
CRP	C reactive protein
CTD	Connective tissue disease
CV	Cardiovascular
CVD	Cardiovascular disease
CYC	Cyclophosphamide
dcSSc	Diffuse cutaneous systemic sclerosis
dSSc	Diffuse systemic sclerosis
DAC	Data Analysis Committee
DLCO	Single breath diffusion capacity
DP	Dorsalis pedis
DSMB	Data Safety and Monitoring Board
eGFR	Estimated glomerular filtration rate
ECG	Electrocardiograph
EMT	Epithelial to mesenchymal trans-differentiation
ENA	Extractable nuclear antigen
ERS	European Respiratory Society
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
EUSTAR	EULAR Scleroderma Trials and Research group
FVC	Forced vital capacity
GCP	Good clinical practice
GIT	Gastrointestinal tract
GFR	Glomerular filtration rate
GORD	Gastro-oesophageal reflux disease

Hb	Haemoglobin
HAQ-DI	Health Assessment Questionnaire - Disease Indicator
HDL	High-density lipoprotein
HRCT	High resolution computed tomography
ISRCTN	International Standard Registry of Controlled Trial Numbers
IB	Investigator brochure
ICH	International Council on Harmonisation
IL	Interleukin
ILD	Interstitial lung disease
IMB	Irish Medicines Board
IV	Intravenous
lcSSc	Limited cutaneous systemic sclerosis
lSSc	Limited systemic sclerosis
LFT	Liver function test
mRSS	Modified Rodnan skin score
MCTD	Mixed connective tissue disease
MHRA	Medicines and Healthcare Regulatory Agency
MI	Myocardial infarction
MMF	Mycophenolate mofetil
MS	Mycophenolate sodium
MTX	Methotrexate
MRC	Medical Research Council
NYHA	New York Heart Association
OR	Odds ratio
PAD	Peripheral arterial disease
PAH	Pulmonary artery hypertension

PAP	Pulmonary artery pressure
PASP	Pulmonary artery systolic pressure
PCI	Percutaneous intervention
PCWP	Pulmonary capillary wedge pressure
PFT	Pulmonary function test
PGI2	Prostacyclin
PI	Principal Investigator
PIL	Patient information leaflet
PT	Posterior tibial
PPI	Proton pump inhibitor
PV	Plasma viscosity
R&D	Research and Development
RAP	Right atrial pressure
RA	Rheumatoid arthritis
RCT	Randomised controlled trial
REC	Research Ethics Committee
RNA	Ribonucleic acid
ROS	Reactive oxygen species
RP	Raynaud’s Phenomenon
RV	Residual volume
RVSP	Right ventricular systolic pressure
SAE	Serious adverse event
SAR	Serious adverse reaction
SMR	Standardised mortality ratio
SRC	Scleroderma renal crisis
SSc	Systemic sclerosis

SUSAR	Suspected unexpected serious adverse reaction
TFR	Tendon friction rubs
TIA	Transient ischaemic attack
TLC	Total lung capacity
TMG	Trial management group
TNF	Tumour necrosing factor
TOE	Trans-oesophageal echocardiography
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction
UK	United Kingdom
WBC	White blood cell
WHO	World Health Organisation

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'Dada Gan Iarracht'

SIGNED DECLARATION

I hereby declare that I, Stephen John McSwiggan, am the sole author of this thesis. All the references cited in this thesis have been consulted by me personally. The work, of which this thesis is a record, has been conducted entirely by me and has not been previously accepted for a higher degree.

Stephen John McSwiggan

7th July 2014

SUPERVISORY STATEMENT

I hereby declare that Stephen John McSwiggan has completed this work in the Vascular and Inflammatory Diseases Research Unit, Division of Medical Sciences, and has fulfilled the conditions of the relevant ordinance and regulations of the University of Dundee, so that he is qualified to submit the following thesis in application for the degree of Doctor of Philosophy (PhD).

Professor Jill JF Belch **Dr Faisel Khan**

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SUMMARY

Background

Systemic sclerosis (SSc) is an autoimmune disease associated with significant mortality and morbidity. Cardiovascular causes are the single largest contributor to premature death. To date, much of the focus on managing the care of SSc patients has concentrated on traditional risk factors related to fibrotic and microvascular dysfunction. There is, however, evidence of a strong cardiovascular component to the disease and points to macrovascular dysfunction as being a key contributor to the premature mortality associated with SSc. This thesis reports on the conduct of a multi-centre, randomised, placebo-controlled clinical trial (the SSTEP Study). The aim of the study was to assess whether oral Iloprost was more effective than placebo in reducing cardiovascular events and disease progression in SSc.

Methods

Two hundred and sixteen patients with systemic sclerosis were recruited, between February 2002 and February 2005, at nine centres in the UK and Ireland. After one month placebo run-in, participants were randomised to either oral Iloprost (50-200mcg daily) or matched placebo. Baseline demographics, disease characteristics and organ screening data were collected, and participants were reviewed annually for endpoint measurements; CV events, SSc disease progression and mortality, with regular safety reviews between these annual visits. Participants were followed up for a period of 4 to 7 years.

Results

Data analysis of the combination of the two measures (survival free from death or a cardiovascular event) demonstrated a trend towards favouring Iloprost over placebo but the difference was not statistically significant (Logrank test: Chi square=0.75, p=0.39). When time to a confirmed cardiovascular endpoint alone was examined there was a suggestion of a benefit from Iloprost, but the difference was again not statistically significant (Logrank test, Chi square =0.82, p=0.37). There was no statistically significant change in the rate at which organ screening endpoints occurred throughout follow-up, and for each endpoint there was no statistically significant difference between results in patients randomised to Iloprost compared to those randomised to placebo. Withdrawal from the treatment to which the patient was randomised was frequent with 97 (45%) of the total participants discontinuing study medication. 'On treatment' analysis, undertaken using the endpoint of death or confirmed cardiovascular endpoint, just failed to show statistical significance at the 5% level (p=0.054).

Conclusion

The results of the SSTEP study showed that there was a trend towards favouring oral Iloprost over placebo in systemic sclerosis, though there was no statistically significant evidence to recommend its use to prevent disease progression. The high rate of withdrawal from both Iloprost and placebo hindered the possibility of demonstrating that Iloprost was effective in this study. It cannot be concluded that it is a useful therapy that may prevent premature mortality or progression to cardiovascular disease in this patient group.

ABSTRACTS AND PRESENTATIONS

The following abstract and presentations have resulted from this work:

Abstracts

Oral presentations

Systemic Sclerosis: Use of iloprost in prevention of cardiovascular disease: preliminary results. *University of Dundee 20th postgraduate symposium* (16th June 2010).

Clinical trial activity in Dundee: commercial and charity sponsored trials, the SSTEP study. *Raynaud's and Scleroderma Association 27th Annual Conference.* Moat House Hotel, Chester (26th Sept 2009).

What can you do to help yourself? Practical advice for managing Raynaud's and SSc. *Dundee Raynaud's and Scleroderma Support group*. Ninewells Hospital, Dundee (16th Jan 2009).

Poster presentations

Systemic Sclerosis Trial of Events and Progression: Progress so far. *University of Dundee Research Nurses Forum,* Ninewells Hospital, Dundee (20th Jan 2010).